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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,123	01/09/2002	Se-Chang Kwon	DE1325	6189

1109 7590 09/21/2007

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
09/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/031,123	KWON ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 August 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: *17,20 and 25*.
   Claim(s) rejected: *1-10,18,19,21-24,26 and 27*.
   Claim(s) withdrawn from consideration: *11-16*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: please see attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

ATTACHMENT TO ADVISORY ACTION

Claims 1-8, 18, 19, 21-24, 26, and 27 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kuga et al. in view of EP 0256843A1 for reasons of record.

Applicant argues that Kuga does not teach how to make a modified hG-CSF lacking an N-terminal methionine and instead suggests use of enzymatic cleavage. This has been fully considered but is not found to be persuasive for the following reasons. While it is true that Kuga's hG-CSF has an N-terminal methionine, Kuga also acknowledges how the N-terminal methionine is disadvantageous at col. 46, li. 29-40. EP 0256843A1 specifically teach how to use the enzymatic cleavage approach suggested by Kuga to make an hG-CSF that lacks the N-terminal methionine at pp. 12-13 and claim 6. Therefore, the combination of references fairly suggested to one of ordinary skill in the art at the time of the invention how to make hG-CSF lacking an N-terminal methionine.

Applicant further urges that the instant claims are distinguished over Kuga because they are directed to a non-glycosylated hG-CSF, unlike the hG-CSF of Kuga et al. This has been full considered but is not found to be persuasive. After careful consideration of the evidence of record and the relevant art, it has been determined that the *E. coli*-produced hG-CSF of Kuga also was not glycosylated as an inherent property of that molecule, since production of mammalian proteins in *E. coli* results in a non-glycosylated product. As evidence of such, Applicant's attention is directed to DeFrees et al. (2006, Glycobiology 16:833-843) who clearly state that several mammalian glycoproteins "such as granulocyte colony stimulating factor (G-CSF), interferon-

alpha2b (IFN-α2b), and granulocyte/macrophage colony stimulating factor (GM-CSF) are naturally *O*-glycosylated human glycoproteins but are manufactured by recombinant expression in *E. coli* as non-glycosylated polypeptides" (p. 833, bottom of right column). The fact that *E. coli*-produced hG-CSF was not glycosylated was also appreciated at the time of the invention by Souza et al. (1986, Science 232:61-65), who explain such at p. 62, top of middle column. Thus, the hG-CSF of Kuga also contained no sugar chain, as specified in the claims.

Claims 9 and 10 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Kuga et al. in view of EP 0256843A1 and further in view of Builder et al. for reasons of record.

Applicant argues that one skilled in the art could not anticipate, predict, or expect from the teachings of Kuga et al., even if combined with the use of *E. coli* thermoresistant enterotoxin II as disclosed in Builder et al., that a modified hG-CSF can be successfully produced from prokaryotic transformants without a Met residue when an appropriate secretory signal peptide is employed. Applicant urges that to suggest otherwise constitutes using impermissible hindsight reconstruction of the claimed invention. This has been fully considered but is not found to be persuasive. Builder et al. successfully used the *E. coli* thermoresistant enterotoxin II signal peptide to express another mammalian growth factor that lacks an N-terminal methionine, IGF-I, in a prokaryotic transformant. Note Rinderknecht et al. (1978, J. Biol. Chem. 253:2769-2776), Figure 1, p. 2771. Such provides a reasonable expectation of success using the

same expression system to obtain a similar mammalian growth factor lacking an N-terminal methionine (hG-CSF). Furthermore, Builder et al. specifically suggest using their system to produce hG-CSF at column 8, line 22.

Applicant argues that they are unaware of any external sources or references that would motivate one of ordinary skill in the art to combine the teachings of Kuga et al. with wither EP 0256843A1 o Builder et al., unless impermissible hindsight is used. this has been fully considered but is not found to be persuasive. It is respectfully submitted that one of ordinary skill in this art would have been aware that recombinant production of mammalian proteins in *E. coli* resulted in non-glycosylated proteins as evidenced by Souza et al. and Rinderknecht et al. Further, one of ordinary skill in this art would have been aware that recombinant production of mammalian proteins in *E. coli* using the enterotoxin II signal peptide would have resulted in successful production despite the lack of an N-terminal methionine as evidenced by Builder et al. Therefore, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ECK

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646